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RISK OF ENDOMETRIAL AND BREAST CANCER IN PATIENTS WITH DIABETES MELLITUS

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Diabetes mellitus patients have metabolic and endocrine alterations that could contribute to an increased incidence of hormone-related cancers. We assessed the incidence of endometrial and breast cancer among 80,005 women and the incidence of breast cancer among 73,847 men (total of 153,852 patients) identified in the Swedish In-patient Register as having been hospitalized for diabetes mellitus in the period 1965–1983. These patients underwent follow-up through 1989 via the Swedish Cancer Register and other nation-wide Swedish registers. The outcome measures were standardized incidence ratios (SIR) based on age-, sex- and calendar period-specific incidence rates from the entire Swedish population. To minimise the effect of selection bias, we excluded from the calculation of incidence ratios the first year of observation and cases diagnosed incidentally at autopsy. Only first cancers were considered for the estimates. A total of 328 endometrial cancers (SIR = 1.8; 95% confidence interval [CI] = 1.6–2.0), 1,145 female breast cancers (SIR = 1.3; 95% CI = 1.2–1.4) and 13 male breast cancers (SIR = 2.0; 95% CI = 1.0–3.4) were observed. We conclude that compared with the general population, patients with diabetes mellitus have an increased incidence of endometrial and breast cancers. *Int. J. Cancer* 71:360–363, 1997.

Although diabetes mellitus has consistently been associated with an increased risk of endometrial cancer in case–control (O'Mara *et al.*, 1985; Brinton *et al.*, 1992; Levi *et al.*, 1993; La Vecchia *et al.*, 1994; Maatela *et al.*, 1994) and cohort (Adami *et al.*, 1991) studies, large prospective studies are needed for a precise estimation of this risk.

We hypothesise that diabetes mellitus may also be associated with breast cancer through several plausible biologic mechanisms. As postulated (Kaaks, 1996; Stoll, 1996), metabolic and endocrine alterations in individuals with insulin resistance might increase the incidence of breast cancer. Two features of non–insulin-dependent diabetes mellitus (NIDDM) have been associated with increased breast cancer risk, namely glucose intolerance and hyperinsulinaemia (Kaaks, 1996; Stoll, 1996). Hyperinsulinaemia is also associated with increased levels of insulin-like growth factors (IGF) in breast tissue, which might act synergistically with an increased estrogenic bioactivity (Stoll, 1996). Patients with diabetes mellitus also have an increased production of reactive oxygen species that could contribute to oxidative damage to DNA and possibly to oncogenesis (Dandona *et al.*, 1996).

To date, case–control and cohort studies have not provided consistent evidence for an association between diabetes mellitus and breast cancer risk (Kaaks, 1996).

We performed a large, population-based cohort study in Sweden to assess the incidence of both endometrial and breast cancer during long-term follow-up of patients with diabetes mellitus.

PATIENTS AND METHODS

Cohort

The cohort was composed of patients identified in the Swedish In-patient Register (The National Board of Health and Welfare, Stockholm, Sweden) with at least 1 admission to the hospital with a discharge diagnosis of diabetes mellitus in 1965–1983. The register was started in 1964–1965, and the estimated coverage of the Swedish population increased from 60% of all hospital admissions in 1969 to 85% in 1983. A detailed description of this register has been published elsewhere (Naessén *et al.*, 1989). In addition to the national registration number, a unique personal identifier assigned to all Swedish residents, each record includes data on hospital department and up to 8 discharge diagnoses for each hospital admission coded according to the 7th revision of the International Classification of Diseases (ICD-7) through 1968 and to the 8th revision (ICD-8) thereafter. Because private in-patient care in Sweden is negligible and patients were not allowed to use public hospitals outside the county, hospital-provided medical services are, in effect, population-based and referable to the county in which the patient lives.

We identified 216,827 records with unique national registration numbers, with at least 1 recorded hospitalization containing a diabetes mellitus diagnosis (ICD-7 code 260, ICD-8 code 250) between 1965 and 1983. Record linkage to the nation-wide registers of the Total Population, Death Register and Population Migration enabled us to exclude 25,415 records with incorrect national registration numbers, *i.e.*, not corresponding to any one living, deceased or emigrated person. Cross-linkage within the In-patient Register identified the first registered admission for diabetes for each unique national registration number.

Follow-up

We obtained information on dates of death for deceased persons from the Death Register and on date of emigration for emigrated persons from the Register of Population Migration. The national Swedish Cancer Register, founded in 1958, is estimated to be 98% complete (Mattsson *et al.*, 1985), and it provided data on prevalent cancer cases at entry into the cohort and incident cancers diagnosed in the cohort during follow-up. The person-time of observation was computed from the date of discharge from the first recorded hospitalization with a diabetes mellitus diagnosis in the In-patient Register until diagnosis of any cancer, emigration, death or end of the observation period (December 31, 1989), whichever occurred first. We excluded 6,606 national registration numbers due to date discrepancies (inconsistency between records) and 14,881 subjects who died on their first recorded hospitalization. Of the remaining 169,925 subjects, 16,073 (9.5%) were excluded from the cancer incidence analysis because of prevalent cancers, which left 153,852 patients who entered the cohort. Of these, 80,005 were women and 73,847 men. The mean duration of follow-up for both sexes was 6.7 years (range 1–24 years). The average calendar year of entry into the cohort was 1977.

Analyses

The Cancer Register (The National Board of Health and Welfare, Stockholm, Sweden) provided a file with diagnosed cancer cases

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categorised according to ICD-7 for the entire period of the study. The expected number of cancers was calculated by multiplying the observed number of person-years by age-, sex- and calendar year-specific cancer incidence rates derived from the entire Swedish population.

We excluded the person-years that elapsed in the first year of follow-up as well a the endometrial and breast cancer cases that were detected during the same period to minimise the possibility of selection bias. Such bias would occur if patients hospitalized for early cancer symptoms were also investigated for diabetes mellitus. As a consequence, 75 women with endometrial cancer, 194 women with breast cancer and 2 men with breast cancer were excluded. To avoid ascertainment bias, cases diagnosed incidentally at autopsy were left out from the observed and expected cases in the incidence analyses (16 endometrial cancers cases and 21 breast cancer cases). Only first primary cancers were considered for the incidence analyses. The mean age at the beginning of follow-up was 64.2 years for women and 59.2 years for men (Table I).

The ICD codes do not distinguish between insulin-dependent diabetes mellitus (IDDM) and NIDDM. However, we made several attempts to separate these diseases through analyses stratified by age at entry into the cohort (<40 years *vs.* ≥40 years), assuming that IDDM would predominate in the younger group, and by birth cohort (born before 1900 *vs.* born during or after 1900), assuming that NIDDM would predominate among those born before 1900 and surviving until 1965. Most members of the cohort probably had NIDDM, as indicated by the mean age at enrollment into the cohort (Table I).

To test the hypothesis that poor diabetic control is associated with an increased cancer risk due to enhanced oxidative damage to DNA (Dandona *et al.*, 1996), patients were classified as ''ever'' or ''never'' being hospitalized for ''classic diabetic complications,'' *i.e.*, recorded hospitalizations at least once for 1 or more of the following discharge diagnoses: diabetic neuropathy (ICD-8 260.49), nephropathy (ICD-8 260.30) or retinopathy (ICD-8 260.21). If a patient was hospitalized for complications after a first recorded hospitalization for diabetes mellitus, person-years before the hospitalization due to the complication were attributed to the non-complication stratum.

The standardized incidence ratios (SIR), defined as the ratio of observed number of cancers to those expected, was used as a measure of relative risk. The 95% confidence interval (CI) of this ratio was calculated on the assumption that the observed number follows a Poisson distribution.

Approval from the Ethics Committee, Uppsala University, and from the Swedish Data Inspection Board were obtained for the linkages between registers necessary to perform this study.

RESULTS

Endometrial cancer

For endometrial cancer, the overall SIR was 1.8 (95% CI = 1.6–2.0), based on 328 cases occurring during 1 to 24 years of follow-up. This excess risk persisted at an essentially similar level throughout the period of follow-up. Women enrolled into the cohort before 40 years of age showed a higher relative risk of endometrial cancer than women enrolled into the cohort after this age, but the difference between the SIRs was not statistically significant ($p = 0.19$). There was also no difference in risk for endometrial cancer between diabetes mellitus patients ever *vs.* those never hospitalized for classic diabetic complications or between those born before or after 1900 (Table II). When 2,423 women with a discharge diagnosis of obesity were excluded from the cohort, only a slight reduction in the relative risk was observed (SIR = 1.7; 95% CI = 1.5–1.9).

Breast cancer

Among women, the overall SIR for breast cancer was 1.3 (95% CI = 1.2–1.4) based on 1,145 observed cases occurring after more than 1 year of follow-up. This excess risk also persisted at a similar level throughout the follow-up period. We found no excess risk among women aged less than 40 years when enrolled into the cohort. There was no statistically significant difference in risk for breast cancer between those ever *vs.* those never hospitalized for classic diabetic complications or when comparing those born before *vs.* after 1900 (Table III).

Among men, the SIR for breast cancer was 2.0 (95% CI = 1.0–3.4) based on 13 observed cases. Eight of these cases occurred between the first and fourth year after the index diabetes mellitus

TABLE I – CHARACTERISTICS OF PATIENTS ASSIGNED A HOSPITAL DISCHARGE DIAGNOSIS OF DIABETES MELLITUS IN SWEDEN BETWEEN 1965 AND 1983, WITH FOLLOW-UP THROUGH 1989

Characteristic[1]	Women	Men
Number of patients	70,110	63,988
Total number of person-years of follow-up	468,497	432,650
Average age at entry into the cohort	64.2	59.2
Average years of follow-up	6.7	6.8
Number of primary cancers		
Endometrial (ICD-7 172)	328	—
Breast (ICD-7 170)	1145	13

[1]Excluding the first year of follow-up (person-years and cases) and cases incidentally diagnosed at autopsy.

TABLE II – STANDARDIZED INCIDENCE RATIOS (SIR) AND 95% CONFIDENCE INTERVALS (CI) FOR ENDOMETRIAL CANCER AMONG 70,110 SWEDISH WOMEN WITH A HOSPITAL DISCHARGE DIAGNOSIS OF DIABETES MELLITUS

	Observed	SIR	CI
Incidence, 1–24 years of follow-up	328	1.8	1.6–2.0
Years of follow-up			
1–4	140	1.9	1.6–2.2
5–9	134	1.9	1.6–2.2
10–24	54	1.6	1.2–2.1
Age at entry into the cohort (years)			
<40	11	2.7	1.3–4.8
≥40	317	1.8	1.6–2.0
Hospitalization for classic diabetic complications[1]			
Ever	28	2.0	1.4–2.9
Never	297	1.8	1.6–2.0
Birth cohort			
<1900	59	1.8	1.4–2.4
≥1900	269	1.8	1.6–2.0

[1]Diabetic retinopathy (ICD-8 260.21), nephropathy (ICD-8 260.30) or neuropathy (ICD-8 260.49).

TABLE III – STANDARDIZED INCIDENCE RATIOS (SIR) AND 95% CONFIDENCE INTERVALS (CI) FOR BREAST CANCER (ICD-7 170) AMONG 70,110 SWEDISH WOMEN WITH A HOSPITAL DISCHARGE DIAGNOSIS OF DIABETES MELLITUS

	Observed	SIR	CI
Incidence, 1–24 years of follow-up	1145	1.3	1.2–1.4
Years of follow-up			
1–4	484	1.4	1.2–1.5
5–9	450	1.3	1.2–1.4
10–24	211	1.2	1.1–1.4
Age at entry into the cohort (years)			
<40	40	1.0	0.7–1.3
≥40	1105	1.3	1.2–1.4
Hospitalization for classic diabetic complications[1]			
Ever	84	1.3	1.0–1.6
Never	1049	1.3	1.2–1.4
Birth cohort			
<1900	279	1.4	1.2–1.5
≥1900	866	1.3	1.2–1.4

[1]Diabetic retinopathy (ICD-8 260.21), nephropathy (ICD-8 260.30) or neuropathy (ICD-8 260.49).

hospitalization (SIR = 2.9; 95% CI = 1.5–5.6). Small numbers prevented further stratified analyses.

When 2,423 women and 1,266 men with a discharge diagnosis of obesity were excluded from the cohort, no changes in the incidence estimates of breast cancer were observed.

DISCUSSION

In this large, population-based cohort study, we found a statistically significant 80% excess incidence of endometrial cancer among patients hospitalized with diabetes mellitus. Assuming that IDDM patients born before 1900 are unlikely to have survived until the enrollment period of our study, those born before 1900 are almost certainly NIDDM patients. Conversely, most patients receiving their diabetes mellitus diagnosis before the age of 40 probably have IDDM. The remaining patients in this cohort represent a mixture of NIDDM and a small proportion of IDDM patients. Except for a higher point estimate of SIR for endometrial cancer in the probable IDDM group, our attempts to distinguish IDDM from NIDDM did not reveal any consistent pattern. Furthermore, women hospitalized with classic diabetic complications presented no statistically significant difference in risk of endometrial cancer compared with those with no recorded hospitalization for these complications. These women were likely to represent patients with poorer metabolic control, leading to higher levels of insulin in NIDDM, and probably more oxidative stress in both types of diabetes mellitus (Dandona *et al.,* 1996).

The excess risk of breast cancer was smaller than that for endometrial cancer. However, similar to endometrial cancer, the increased risk of breast cancer persisted throughout the follow-up period. Stratified analyses seemed to indicate that the excess risk was confined to patients with NIDDM, but the SIR for the probable IDDM group was based only on 40 cases. We also found a clear excess number of breast cancers in men.

Even in the absence of a causal relationship, a positive association between diabetes mellitus and endometrial cancer might occur due to shared risk factors. In particular, obesity has been reported as increasing the risk of both these diseases. When we excluded from the analysis patients with a discharge diagnosis of obesity, the risk estimates did not change substantially (data not shown). However, we cannot exclude completely the potential role of obesity as a confounder in our analysis. In previous studies, the association between diabetes mellitus and uterine cancer was observed in lean women, suggesting independent effects of obesity and diabetes on, for example, sex hormone metabolism (O'Mara *et al.,* 1985).

Information on use of oral contraceptives, hormone replacement therapy and reproductive history were not available in the registries. However, women born before 1900, for whom exposure to oral contraceptives or hormonal replacement therapy is unlikely, exhibited the same excess risk as those born thereafter. Estrogen replacement may be prescribed more restrictively to patients with diabetes mellitus than to women in general (Nyholm *et al.,* 1993). Despite the postulated effects of these hormones on glucose tolerance, there is no evidence that post-menopausal hormone therapy is associated with an increase in the incidence of NIDDM (Manson *et al.,* 1992*a*). The use of combined estrogen-progestin high-dose oral contraceptives may increase the risk of impaired glucose tolerance, but this effect is reversible within 6 months of discontinuing oral contraceptives, and the development of diabetes mellitus in high-dose oral contraceptive users is rare (Harvengt, 1992). Parity was not associated with NIDDM in previous studies (Manson *et al.,* 1992*b*); therefore, it is not a probable confounder of the association between diabetes mellitus and endometrial and breast cancers.

Women with IDDM seem to have a higher probability of delayed menarche, particularly when IDDM develops before menarche (Yeshaya *et al.,* 1995). Because the age at menarche is inversely associated with the risk of endometrial (McPherson *et al.,* 1996) and breast (Adami *et al.,* 1995; Kaaks, 1996) cancers, the lack of control of this variable in our analyses may have led to an underestimation of the SIRs. Women with IDDM are also at higher risk for having menstrual disturbances, such as amenorrhea, and fertility disorders (Yeshaya *et al.,* 1995). However, we do not expect that this would have changed our results substantially, because the proportion of IDDM in our cohort is probably small. Therefore, confounding by reproductive history, use of oral contraceptives or hormone replacement therapy are not likely to explain our findings.

Several possible mechanisms could hypothetically explain the association of diabetes mellitus with endometrial and breast cancer risks. Both are hormone-related malignancies, and diabetes mellitus may cause hormonal alterations that promote the development of these cancers. Compared with healthy women, diabetes mellitus patients have been found to have higher levels of circulating estrogens and decreased levels of luteinizing hormone and follicle stimulating hormone in the post-menopausal period (Quinn *et al.,* 1981). Insulin stimulates androgen synthesis in the ovarian stroma; thus, it decreases levels of sex hormone binding globulin (SHBG) and increases levels of free estradiol (Kaaks, 1996). Several studies have reported an inverse association between plasma levels of sex hormone binding globulin and breast cancer risk (Kaaks, 1996). Women with hormone-dependent tumors have been reported to have reduced glucose tolerance and an elevation of plasma insulin levels (Maggino *et al.,* 1993). It has also been hypothesised that insulin may exert a direct influence through estrogen receptors, altering the biologic behaviour of steroid hormone target tissues. Thus, diabetes mellitus has been suggested to alter the outcome of estrogen receptor-positive tumors, such as breast or endometrial carcinomas (Chaudhuri *et al.,* 1986).

Another possible mechanism by which diabetes mellitus might increase cancer risk is through oxidative damage to DNA. Dandona *et al.* (1996) reported a significantly higher median concentration of 8-hydroxydeoxyguanosine in mononuclear cells, an indicator of oxidative damage to DNA, with increased generation of reactive oxygen species in IDDM and NIDDM patients compared with healthy control individuals. They postulated that oxidative damage to enzymes involved in the repair of DNA damage could enhance oncogenesis.

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